

Hyperprolactinemia in antipsychotic-naïve patients with first-episode psychosis

A. Riecher-Rössler^{1*}, J. K. Rybakowski², M. O. Pflueger¹, R. Beyrau³, R. S. Kahn⁴, P. Malik⁵, W. W. Fleischhacker⁵; and the EUFEST Study Group†

¹University of Basel Psychiatric Clinics, Basel, Switzerland

²Department of Adult Psychiatry, Poznan University of Medical Sciences, Poznan, Poland

³Department of Clinical Chemistry, University Hospital Basel, Switzerland

⁴Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, The Netherlands

⁵Department of Biological Psychiatry, Medical University Innsbruck, Austria

Background. Hyperprolactinemia is frequent in patients with schizophrenic psychoses. It is usually regarded as an adverse effect of antipsychotics but has recently also been shown in patients without antipsychotic medication. Our objective was to test whether hyperprolactinemia occurs in antipsychotic-naïve first-episode patients (FEPs).

Method. In the framework of the European First Episode Schizophrenia Trial (EUFEST), 249 out of 498 FEPs were eligible for this study, of whom 74 were antipsychotic naïve. All patients were investigated regarding their serum prolactin levels with immunoassays standardized against the 3rd International Reference Standard 84/500.

Results. Twenty-nine (39%) of the 74 antipsychotic-naïve patients showed hyperprolactinemia not explained by any other reason, 11 (50%) of 22 women and 18 (35%) of 52 men.

Conclusions. Hyperprolactinemia may be present in patients with schizophrenic psychoses independent of antipsychotic medication. It might be stress induced. As enhanced prolactin can increase dopamine release through a feedback mechanism, this could contribute to explaining how stress can trigger the outbreak of psychosis.

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Introduction

Hyperprolactinemia is frequently found in patients with schizophrenic psychoses and is usually considered to be an adverse effect of antipsychotic medication. It occurs with most conventional antipsychotics but also during treatment with some new-generation antipsychotics and is mainly associated with D₂ receptor affinity (Bushe *et al.* 2008; Fitzgerald & Dinan, 2008; Riecher-Rössler *et al.* 2009). However, there have also been recent reports on hyperprolactinemia in antipsychotic-free patients with first-episode psychosis (Kahn *et al.* 2008; Aston *et al.* 2010; Garcia-Rizo *et al.* 2012) and in patients with an at-risk mental state (ARMS) for psychosis (Aston *et al.* 2010).

Prolactin is a peptide hormone secreted mainly by prolactin-producing cells of the anterior pituitary.

Its main function is to induce lactation. The control of prolactin production and secretion is complex (Fig. 1). The main regulatory mechanism is inhibition by dopamine, which is synthesized in neurons of the hypothalamus and then secreted through portal blood into the anterior pituitary, where it exerts its actions on prolactin-producing cells through D₂ receptors. Dopamine is thus the main prolactin-inhibiting factor (PIF) (Fitzgerald & Dinan, 2008; Low, 2008; Prabhakar & Davis, 2008). Dopamine tonically inhibits prolactin release. A negative feedback control of prolactin secretion is mediated by a short loop mechanism to the hypothalamus. Prolactin activates prolactin receptors leading to increased dopamine synthesis and release (Fitzgerald & Dinan, 2008; Low, 2008).

Prolactin secretion is stimulated by sucking but also by stress (Low, 2008; Prabhakar & Davis, 2008). Prolactin-releasing factors (PRFs) probably include thyrotropin-releasing hormone (TRH), vasoactive intestinal polypeptide (VIP) and oxytocin. Estrogens also stimulate prolactin synthesis through a positive feedback loop, and indirectly through their anti-dopaminergic properties (Low, 2008).

* Address for correspondence: Prof. Dr med. A. Riecher-Rössler, Center for Gender Research and Early Detection, University of Basel Psychiatric Clinics, c/o University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland.

(Email: anita.riecher@upkbs.ch)

† Members of the EUFEST Study Group are listed in the Appendix.

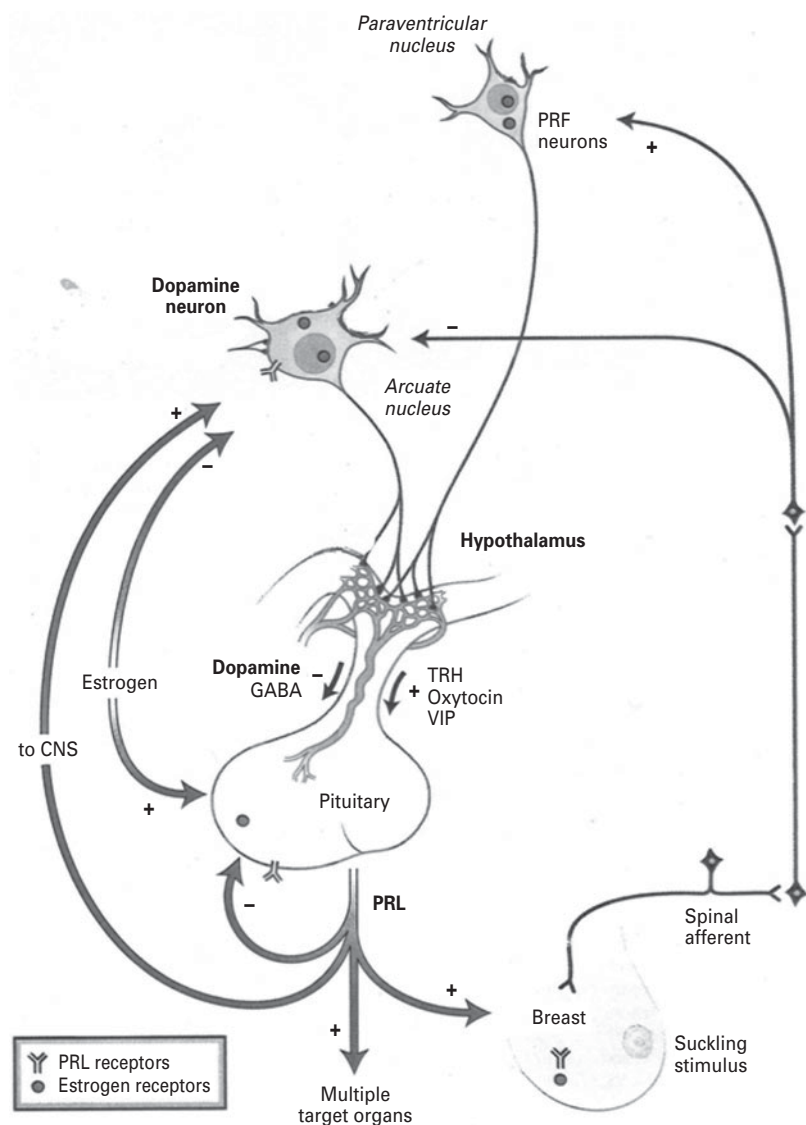


Fig. 1. Control of prolactin (PRL) production and secretion. PRF, prolactin-releasing factor; TRH, thyrotropin-releasing hormone; VIP, vasoactive intestinal polypeptide; GABA, γ -aminobutyric acid; CNS, central nervous system. Reproduced, with permission from Elsevier, from W. J. Low (2008). *Neuroendocrinology*. In *Williams Textbook of Endocrinology* (ed. H. M. Kronenberg, S. Melmed, K. S. Polonsky and P. R. Larsen), 9th edn, pp. 85–295. W.B. Saunders Co.: Philadelphia, PA.

Hyperprolactinemia (i.e. prolactin serum values above the normal range) can be caused by many physiological processes, by psychological distress (for review see Low, 2008; Prabhakar & Davis, 2008), and also by pathological conditions such as prolactin-secreting tumors. Thus, hyperprolactinemia in patients with schizophrenic psychoses may not only be treatment related but also possibly disease related.

Hyperprolactinemia can suppress gonadal function with a reduced physiological production of estrogens and testosterone (Dickson *et al.* 2000; Prabhakar & Davis, 2008). This can have serious clinical consequences (e.g. sexual dysfunction, infertility or

osteopenia) in both men and women (for review see (Haddad & Wieck, 2004; Miller, 2004; Prabhakar & Davis, 2008; Riecher-Rössler *et al.* 2009).

We therefore aimed to determine, in the framework of the European First Episode Schizophrenia Trial (EUFEST; Fleischhacker *et al.* 2005; Kahn *et al.* 2008), whether antipsychotic-naïve first-episode patients (FEPs) show hyperprolactinemia and, if so, whether it is associated with factors such as pretreatment, age, gender or severity of illness. To our knowledge this is one of the largest samples of antipsychotic-naïve first-episode psychosis patients studied regarding these issues.

Method

Data were obtained as part of the EUFEST, the methodology of which has been described in more detail in previous publications (Fleischhacker *et al.* 2005; Kahn *et al.* 2008). A total of 50 centers participated. Eligible patients were aged 18–40 years and met DSM-IV criteria for schizophrenia, schizophreniform disorder or schizo-affective disorder. Onset of positive symptoms had to have occurred no more than 2 years before study entry, and no more than 6 weeks of lifetime exposure to antipsychotics was allowed. After complete description of the study to the subjects, written informed consent was obtained. The trial complied with the Declaration of Helsinki, and was approved by the ethics committees of the participating centers. The Julius Center for Health Sciences and Primary Care monitored the trial according to Good Clinical Practice and International Conference on Harmonisation guidelines.

We included 249 patients from the EUFEST sample (total 498 patients) in the current study. The remaining 249 patients were excluded for the following reasons: in 222 it could not be safely confirmed that they had had their blood samples for prolactin drawn before having received their first antipsychotic medication, 21 had unknown previous medications apart from antipsychotics, and six were non-Caucasian. The latter were excluded as there is some evidence that there might be ethnic differences regarding the hormonal response to psychological stressors (Chong *et al.* 2008).

Baseline data included demographics, diagnosis, treatment setting, psychopathology [Positive and Negative Syndrome Scale (PANSS); Kay *et al.* 1987], severity of illness [Clinical Global Impressions (CGI) scale; Guy, 1976], and other parameters described in the original papers. Pretreatment history was ascertained by questioning patients and significant others, in addition to reviewing available charts.

Prolactin measurements

In each center, immunoassays were used for prolactin measurements, which were standardized against the 3rd International Reference Standard 84/500. The lower and upper reference limits were calculated as the 5th and 95th percentiles. Hyperprolactinemia in this reference is defined as a value above the 95th percentile, that is >0.38 U/l in men and >0.53 U/l in women. To convert values from ng/ml to U/l we used a conversion factor of 0.0212 (Kahn *et al.* 2008).

Statistical methods

The R environment for statistical computation was used to analyze the EUFEST dataset (R Development

Core Team, 2011). Simple parametric and non-parametric statistical tests, such as the Mann–Whitney *U* test and the Student *t* test, were performed to analyze group differences. χ^2 tests and Fisher's exact tests were applied wherever count data were analyzed.

Log-transformed prolactin values were modeled by age, sex and PANSS positive/negative score to account for the influence of relevant variables. A generalized linear model (GLM) approach was adopted, specified by a log link function and gamma family distribution. As the mean function indicates a squared relationship between mean log prolactin and its standard deviation, the assumption of an exponential residual distribution seems to be justified and hence the choice of a GLM belonging to the gamma family. An analysis of deviance was performed to determine a particular factor's contribution in explaining prolactin deviance [a concept functional equivalent to variance in ordinary least squares analysis but specific to GLMs and other modern approaches in linear modeling].

Results

Of the 249 FEP patients with reliable records on medication before prolactin measurements, 74 (52 men and 22 women) were naïve for the intake of any antipsychotic medication. Clinical and demographic characteristics of the 74 antipsychotic-naïve and the 175 not-naïve patients are summarized in Table 1.

Hyperprolactinemia in antipsychotic-naïve patients

As expected, a high proportion of the patients with prior or current intake of antipsychotics showed hyperprolactinemia (i.e. levels above the upper limit of the normal range). However, 30 (40.5%) of the 74 antipsychotic-naïve patients also showed hyperprolactinemia: 11 (50%) of the 22 women and 19 (36.5%) of the 52 men.

The mean prolactin values were also strongly elevated not only in the non-naïve but also in the antipsychotic-naïve patients, and the elevation was especially high in women. Table 2 shows the proportion of patients with hyperprolactinemia in both groups according to gender, along with the mean prolactin values.

For further analyses, unless stated otherwise, we focused on the antipsychotic-naïve sample.

Influence of other previous medications

Of the 30 antipsychotic-naïve patients with hyperprolactinemia, 20 had taken some other medication: benzodiazepines ($n=13$), biperiden ($n=3$), pridinol

Table 1. Sociodemographic and clinical characteristics of antipsychotic-naïve versus non-naïve first-episode patients (FEPs)

	Antipsychotic naïve (<i>n</i> =74)	Antipsychotic non-naïve (<i>n</i> =175)	Total (<i>n</i> =249)	<i>p</i>
Men/women, <i>n</i> (%)	52 (70)/22 (30)	105 (60)/70 (40)	157 (63)/92 (37)	0.151 ^a
Age (years), mean±s.d.	25.8±2.8	26.0±5.5	25.9±5.5	0.739 ^b
Years of education, mean±s.d.	12.8±2.8	12.6±3.1	12.7±3.0	0.376 ^b
Diagnosis, <i>n</i>				
Schizophrenic psychosis	46	84	30	0.106 ^c
Schizo-affective psychosis	6	15	21	
Schizophreniform disorders	22	76	98	

s.d., Standard deviation.

^a Fisher's exact test for count data.^b Mann-Whitney *U* test for ranked data.^c χ^2 test for contingency tables.**Table 2.** Hyperprolactinemia and prolactin values of antipsychotic-naïve versus non-naïve patients with first-episode psychosis

	Antipsychotic naïve			Antipsychotic non-naïve		
	Men (<i>n</i> =52)	Women (<i>n</i> =22)	Total (<i>n</i> =74)	Men (<i>n</i> =105)	Women (<i>n</i> =70)	Total (<i>n</i> =175)
Proportion of patients with hyperprolactinemia ^a , <i>n</i> (%)	19 (36.5)	11 (50.0)	30 (40.5)	75 (71.4)	52 (74.3)	127 (72.6)
Prolactin (U/l) blood levels						
Mean±s.d.	0.37±0.32	0.98±0.94	0.55±0.64	0.83±0.91	1.60±1.44	1.14±1.21
Median	0.26	0.58	0.34	0.68	1.16	0.80
Range	0.04–1.50	0.11–3.29	0.04–3.29	0.00–8.58	0.10–6.66	0.00–8.58
Men versus women						
Mann-Whitney <i>U</i> test	850.5			4956.0		
<i>p</i> value	<0.001			<0.001		

s.d., Standard deviation.

^a Normal values: men<0.38 U/l; women<0.53 U/l.

(*n*=2), hydroxyzine (*n*=1), propranolol (*n*=1), metoclopramide (*n*=1), cetirizine (*n*=1), omeprazol (*n*=1) and sulfacetamide (*n*=1). None of the antipsychotic-naïve women had taken oral contraceptives. There was no significant difference in prolactin values between the 20 patients with previous medication (mean 1.22±0.86 U/l) and the 10 who were completely medication naïve (mean 0.70±0.30 U/l, Mann-Whitney *U*=64, *p*=0.118). Only one of these patients had taken drugs known to increase prolactin (metoclopramide and omeprazol). For further analyses we excluded this patient. We were thus left with 29 out of 74 (39.2%) FEP patients whose hyperprolactinemia could not be explained by antipsychotics or any other medication.

Influence of age and gender

There was no significant age difference between the 29 antipsychotic-naïve patients with unexplained hyperprolactinemia (mean age 25.1±5.4 years) and the 44 antipsychotic-naïve with normal prolactin values (mean age 26.2±5.7 years) (*t*=0.8, *df*=72, *p*=0.412), but there were significant gender differences. Antipsychotic-naïve women had higher prolactin values than men, and the range of values was much larger in the female patients (Fig. 2).

Influence of symptomatology

We also tested whether hyperprolactinemia was associated with the severity of psychopathological

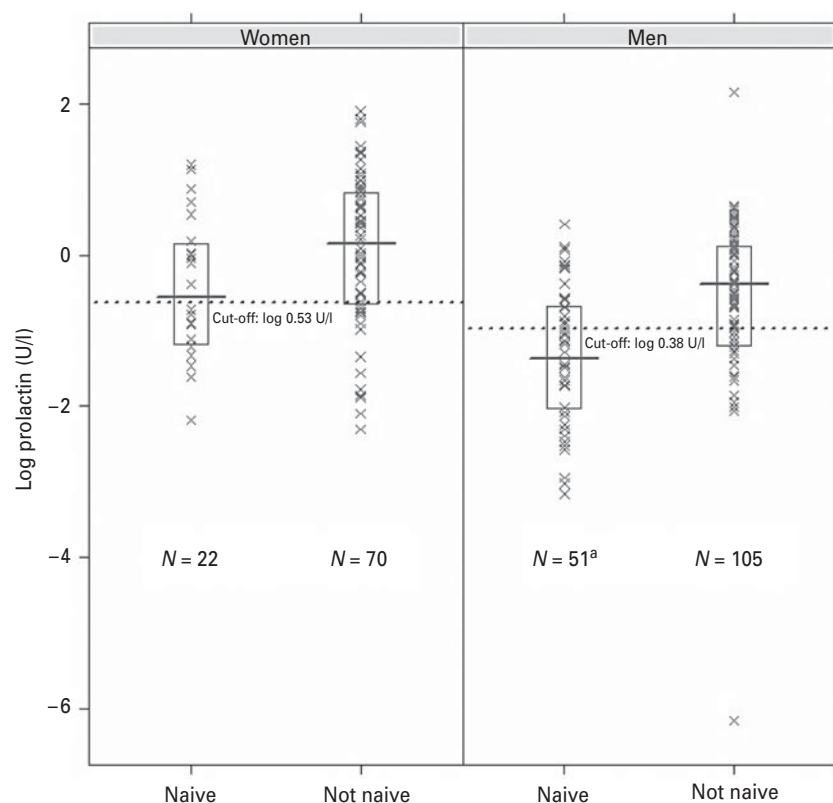


Fig. 2. Prolactin values of patients with first-episode psychosis, naïve and not naïve for antipsychotics, differentiated by gender. Log prolactin levels depend on gender and neuroleptic treatment. Dotted lines indicate a gender-specific cut-off value. Values above this line represent hyperprolactinemia. The boxes surrounding some of the values comprise all values that fall within the first and third quartiles. The horizontal line that is approximately centered within the box corresponds to the median of the particular subsample. ^a After exclusion of one man (see text).

symptoms and/or diagnostic subtype in antipsychotic-naïve patients. Table 3 shows the different PANSS and CGI scores and also specific diagnoses for all antipsychotic-naïve patients, comparing the groups with and without unexplained hyperprolactinemia. There was no diagnostic subtype disproportionately more frequently affected by hyperprolactinemia. Patients with hyperprolactinemia did not differ from patients without hyperprolactinemia in terms of the severity of psychopathological symptoms. Furthermore, there was no correlation of log prolactin values with the total CGI score (Spearman's $\rho=0.02$, $p=0.850$), the PANSS positive score ($r=0.04$, $t_{72}=0.31$, $p=0.756$) or the PANSS negative score ($r=0.11$, $t_{72}=0.95$, $p=0.345$). Additionally, we tested the correlation with the anxio-depressive dimension of the PANSS according to El Yazaji *et al.* (2002), and this was also not significant ($r=0.04$, $t_{72}=0.30$, $p=0.763$).

GLM

In a next step we analyzed the factors potentially influencing prolactin levels, such as sex, age and

severity of psychopathology, that is PANSS positive and negative scores, within the 73 antipsychotic-naïve patients. Using an analysis of deviance of a GLM, we entered age, gender and the PANSS positive and negative scores into the model.

Age and the PANSS positive score did not contribute to explaining a significant amount of variance of the data. However, there were significant main effects of gender ($\chi^2=24.9$, $df=1$, $p<0.001$) and the PANSS negative score ($\chi^2=4.6$, $df=1$, $p=0.032$), and an interaction of gender with the PANSS negative score ($\chi^2=7.9$, $df=1$, $p=0.005$). The mean prolactin level in women with an average negative symptom load (PANSS negative) amounted to 0.98 U/l. By contrast, the mean prolactin level in men was only 37% of the value seen in women. The negative symptoms (PANSS negative) yielded a differential effect on the prolactin level depending on gender: whereas an increasing value of the PANSS negative score was strongly associated with a decreased prolactin level in women (-7% /scale unit PANSS negative), a slightly inverse relationship was found in men ($+3\%$ /unit PANSS negative).

Table 3. Psychopathological symptoms of antipsychotic-naïve first-episode patients (FEPs) with and without unexplained hyperprolactinemia (HP)

	No HP (<i>n</i> =44)	Unexplained HP (<i>n</i> =29) ^a	Total (<i>n</i> =73) ^a	Statistics
Men/women, <i>n</i> (%)	33 (65)/11 (50)	18 (35)/11 (50)	51 (100)/22 (100)	<i>p</i> =0.300
Age (years), mean (s.d.)	26.2 (5.7)	25.3 (5.3)	25.8 (5.6)	<i>t</i> ₇₁ =0.66, <i>p</i> =0.512 ^b
PANSS, mean (s.d.)				
Positive score	20.9 (6.2)	21.0 (5.7)	20.9 (6.2)	<i>t</i> ₇₁ =0.08, <i>p</i> =0.931 ^b
Negative score	18.6 (8.2)	21.2 (7.1)	21.3 (6.0)	<i>t</i> ₇₁ =1.40, <i>p</i> =0.167 ^b
Anxio-depressive dimension ^c	9.8 (3.4)	9.8 (3.8)	9.8 (3.5)	<i>t</i> ₇₁ =0.09, <i>p</i> =0.931 ^b
CGI, <i>n</i> (%)				
Borderline mentally ill	2 (5)	0 (0)	2 (3)	<i>p</i> =0.514 ^d
Mildly ill	1 (2)	2 (7)	3 (4)	<i>p</i> =0.559 ^d
Moderately ill	13 (30)	8 (28)	21 (28)	<i>p</i> ≈1.00 ^d
Markedly ill	23 (52)	14 (48)	38 (51)	<i>p</i> =0.813 ^d
Severely ill	5 (11)	5 (17)	10 (14)	<i>p</i> =0.505 ^d
Diagnostic subtype, <i>n</i> (%)				
Paranoid	22 (50)	17 (59)	39 (53) ^e	<i>p</i> =0.485 ^d
Schizophreniform	15 (34)	7 (24)	22 (30) ^e	<i>p</i> =0.440 ^d
Schizo-affective	3 (7)	3 (10)	6 (8) ^e	<i>p</i> =0.676 ^d
Undifferentiated	4 (9)	2 (7)	6 (8) ^e	<i>p</i> ≈1.00 ^d

PANSS, Positive and Negative Symptom Scale; CGI, Clinical Global Impression; s.d., standard deviation.

^a One patient with intake of prolactin-increasing medication (metoclopramide and omeprazol) was excluded.

^b Two-sample Student's *t* test.

^c PANSS items G1, G2, G3, G6.

^d Fisher's exact test for count data.

^e Percentages do not add up to 100% due to rounding errors.

Clinical sequelae

With regard to potential clinical sequelae of hyperprolactinemia, patients were specifically asked about galactorrhea or amenorrhea. None of the antipsychotic-naïve patients suffered from galactorrhea and only two of the women had amenorrhea, both in the group with hyperprolactinemia.

Discussion

We have studied 74 antipsychotic-naïve FEPs with psychosis within the EUFEST study (Fleischacker *et al.* 2005; Kahn *et al.* 2008). Twenty-nine (39.2%) of these FEPs showed hyperprolactinemia unexplained by any medication or other known influence. To our knowledge this is one of the largest samples of antipsychotic-naïve FEP patients studied regarding this issue. Our findings indicate that hyperprolactinemia in FEP is not necessarily only caused by antipsychotics, but might also be a pre-existing condition in some patients. This corroborates a previous finding from the Basel early-detection-of-psychosis (FEPsY) study (Aston *et al.* 2010), in which hyperprolactinemia was found in 33% of all antipsychotic-naïve

FEP patients, and even in 24% of antipsychotic-naïve patients with an ARMS for psychosis. Similarly, Garcia-Rizo *et al.* (2012) have recently reported higher prolactin concentrations in 33 newly diagnosed antipsychotic-naïve patients with non-affective psychosis compared to 33 matched controls in a well-controlled study. Guest *et al.* (2011) have also reported elevated prolactin concentrations in the blood of 236 first-episode and recent-onset patients with schizophrenic psychoses compared to 230 matched controls. Patients were antipsychotic naïve or antipsychotic free for at least 6 weeks. Segal *et al.* (2004) only found higher prolactin levels in the disorganized subtype of schizophrenic psychoses. Their sample consisted of first-episode and recurrent patients, both unmedicated. Meltzer *et al.* (21) and Kuruvilla *et al.* (22) were not able to demonstrate differences in mean prolactin values between smaller samples of newly admitted unmedicated schizophrenic psychoses patients and healthy controls. However, the prevalence of hyperprolactinemia (i.e. the proportion of patients with levels above the norm) was not reported in their studies and mean values might not be as informative.

It has previously been suggested that hyperprolactinemia may have been present before the introduction

of antipsychotics in some patients with schizophrenic psychoses (Riecher-Rössler & Häfner, 1993; Riecher-Rössler *et al.* 1998). Indirect evidence for this stems from earlier observations of gonadal dysfunction and hypoestrogenemia in unmedicated patients with schizophrenic psychoses. Both suppression of gonadal function and suppression of estrogen production are well known consequences of hyperprolactinemia and both have been described as early as at the beginning of the last century, when antipsychotics had not yet been developed (for review see Riecher-Rössler & Häfner, 1993; Riecher-Rössler *et al.* 1998). Thus, Kraepelin (1909–1915) and Kretschmer (1921) had already reported that many women with schizophrenic psychoses showed physical signs indicating ‘insufficient functioning of the sexual glands’ with ‘hypoestrogenism’. In the 1930s, studies analyzing estrogen levels in blood and urine found decreased estrogen levels in most in-patients with schizophrenic psychoses (Riecher-Rössler & Häfner, 1993; Riecher-Rössler *et al.* 1998). Again, antipsychotics were not available then. Prolactin levels were not measured in those days.

Our findings are also in line with recent MRI findings that showed an increased pituitary volume in antipsychotic-free FEP patients and even in patients with an ARMS for psychosis, especially in those with a later transition to frank psychosis (Garner *et al.* 2005; Pariante, 2008; Büschlen *et al.* 2010; Walter *et al.* 2012), although there is a recent study at odds with this (Klomp *et al.* 2012). As prolactin production in the pituitary is known to be associated with an enlargement of the gland (MacMaster *et al.* 2007), this could theoretically indicate increased prolactin production during emerging psychosis.

Potential clinical implications

Our findings, if confirmed, would have implications for research and also for clinical practice. Hyperprolactinemia can have many adverse clinical effects (Riecher-Rössler *et al.* 2009). Not only can it lead to galactorrhea, but it can also suppress the activity of the hypothalamic–pituitary–gonadal (HPG) axis and gonadal function, leading to a reduced physiological production of estrogens and testosterone (Dickson *et al.* 2000; Prabhakar & Davis, 2008). It may cause amenorrhea and menstrual irregularities in women and erectile dysfunction, along with ejaculatory problems and reduced spermatogenesis, in men. In both genders it can be associated with emotional lability, loss of libido, orgasmic dysfunction and infertility (Haddad & Wieck, 2004; Miller, 2004; Prabhakar & Davis, 2008; Riecher-Rössler *et al.* 2009). As was shown in the total sample of all FEPs of the EUFEST study, higher prolactin plasma levels predict amenorrhea in

women and erectile and ejaculatory dysfunction in men (Malik *et al.* 2011). Chronic hyperprolactinemia has also been associated with osteopenia and osteoporosis (O’Keane & Meaney, 2005) and an increase in the risk of bone fracture (Howard *et al.* 2007), although exposure to prolactin-increasing antipsychotics in one study was not found to be related to bone mineral density (Hummer *et al.* 2005). Finally, there has been some discussion about a possible relationship between hyperprolactinemia and a slightly increased risk for breast cancer (Prabhakar & Davis, 2008; Bushe *et al.* 2009).

Most of the mentioned sequelae of hyperprolactinemia are indirect effects caused by the suppression of gonadal estrogen and testosterone production. Only a few, such as galactorrhea, are direct effects of hyperprolactinemia (Riecher-Rössler *et al.* 2009). The potentially increased risk of breast cancer is also thought to be such a direct effect. These direct effects have mainly been documented in patients with other causes of high prolactin levels, such as prolactinoma, which lead to considerably higher levels of plasma prolactin than those reported here.

From an endocrinological point of view, prolactin levels should be measured before commencing antipsychotic treatment to ensure that hyperprolactinemia is not a pre-existing condition, which would need thorough investigation. Blood samples should be taken in a standardized manner (in the morning between 08:00 and 10:00 h, without any stressful influences, etc.). If hyperprolactinemia is found and deemed not to be drug related, other causes such as thyroid hypofunction or tumors in the area of the pituitary need to be excluded. Potential adverse clinical sequelae should be treated if hyperprolactinemia is persisting and cannot be treated causally.

Potential research implications

Besides potential clinical consequences, our findings may also have implications for research. It might be that, in antipsychotic-naïve patients with prodromal states or first-episode psychosis, hyperprolactinemia is caused by psychological distress associated with the (emerging) illness. It is well known that stress can activate not only cortisol but also prolactin secretion (Low, 2008; Prabhakar & Davis, 2008). The increased pituitary volumes seen in these patients might be due not only to an increase in the production of adrenocorticotrophic hormone (ACTH), as suggested previously (Pariante, 2008), but also to an increase in the production of prolactin in the pituitary (MacMaster *et al.* 2007).

Furthermore, it might be speculated that stress-induced hyperprolactinemia plays a role in triggering the outbreak of acute psychotic symptomatology

because hyperprolactinemia induces the production of prolactin-inhibiting factor (PIF), which is more or less identical with dopamine (Low, 2008).

Dopaminergic transmission is well known to be increased in acutely psychotic patients and even in people at risk for psychosis (Howes & Kapur, 2009). Furthermore, stress in such individuals has been linked to both an increase of symptoms and an increase in dopaminergic indices (van Winkel *et al.* 2008; Howes & Kapur, 2009; van Os *et al.* 2010; Mizrahi *et al.* 2012). It is accepted that different forms of stress can enhance the risk for psychosis and may trigger its outbreak acutely (Phillips *et al.* 2006; van Winkel *et al.* 2008; Howes & Kapur, 2009; van Os *et al.* 2010). This has been integrated into an 'advanced' dopamine hypothesis as the final common pathway for psychosis (Howes & Kapur, 2009). However, the exact mechanisms of how stress influences dopaminergic neurotransmission are not yet completely understood (Phillips *et al.* 2006; van Winkel *et al.* 2008; Howes & Kapur, 2009; Ungless *et al.* 2010; van Os *et al.* 2010).

Ungless *et al.* (2010), in a review of the effects of stress on dopamine neurons, state that 'a major target of stress, and stress-related hormones in particular, are fast excitatory and inhibitory synapses made onto dopamine neurons'. This is where prolactin, which also serves as a stress hormone, may play a possible role in the pathogenesis of (emerging) psychosis as it can directly enhance dopamine levels through a feedback mechanism (Fitzgerald & Dinan, 2008; Low, 2008) (see Fig. 1). Stress can, among other factors, induce hyperprolactinemia, which in turn, as a regulatory mechanism to down-regulate prolactin secretion, induces an increase in PIF (i.e. dopamine). This increase in dopamine would then be able to trigger psychotic symptoms in individuals vulnerable for psychosis. This would mean that the tuberoinfundibular dopamine pathway may be involved in the pathogenesis of schizophrenic psychoses, and not just the mesolimbic and mesocortical pathways as hypothesized prominently in the literature.

This extension of the stress–dopamine hypothesis could help to explain the well-known fact that stress can trigger the outbreak of psychotic symptoms. It might also help to explain why many patients develop schizophrenic psychoses during periods of their lives with strong fluctuations of sex hormones and prolactin, such as during adolescence or, in women, during the postpartum or perimenopausal period (Häfner *et al.* 1993; Riecher-Rössler & Häfner, 1993; Riecher-Rössler *et al.* 1994, 1998).

Of note, hyperprolactinemia and also the increase in the pituitary volume found in our and other studies (Büschen *et al.* 2010) have been demonstrated predominantly in women. At the same time, it has been

shown that women have a stronger prolactin response to antipsychotics (Yasui-Furukori *et al.* 2010). Both findings might be explained by the fact that estrogens sensitize the pituitary to release prolactin (Fitzgerald & Dinan, 2008; Low, 2008). In this context it is also of interest that men and women react differently to stress (Kirschbaum *et al.* 1999).

We could not confirm our hypothesis that prolactin levels are associated with the severity of positive psychotic symptomatology. However, we did find a gender difference regarding negative symptoms. More negative symptoms were related to lower prolactin levels in antipsychotic-naïve women but to higher levels in antipsychotic-naïve men. These gender differences are difficult to explain. It is possible that the intense stress reaction in women with a very high rise of prolactin is attenuated by negative symptoms such as affective flattening.

However, our contrasting finding in men is in accordance with that of Akhondzadeh *et al.* (2006), who found a positive correlation between prolactin plasma levels and negative subscale scores in male patients with chronic schizophrenia. At the same time, their patients had low testosterone levels, which might indicate that hyperprolactinemia-induced suppression of gonadal function with a decrease in testosterone production can result in an increase of negative symptoms. This might open up new therapeutic options with adjunctive testosterone in negative symptoms (Akhondzadeh *et al.* 2006), similar to the adjunctive treatment with estrogens for positive symptoms (for review see Riecher-Rössler & de Geyter, 2007; Riecher-Rössler & Kulkarni, 2011).

There are also genetic links between prolactin and schizophrenic psychoses. The prolactin gene has been mapped to chromosome 6p21 (Evans *et al.* 1989) and this region has long been discussed as a susceptibility locus for schizophrenic psychoses genes (Schwab *et al.* 2003; Tochigi *et al.* 2004; Roig *et al.* 2007). Stevens *et al.* (2001) identified a functional polymorphism –1149 G/T (rs1341239) of the prolactin gene, where the G allele has been associated with higher promoter activity of the gene and a greater increment of prolactin mRNA. In a first study of this polymorphism, a significant preponderance of this allele was found in patients with schizophrenic psychoses compared to healthy controls (Rybakowski *et al.* 2011). It could therefore be hypothesized that individuals with a preponderance of the G allele react more strongly to stress and thus show a higher risk of psychotic breakdown.

Limitations

We cannot completely rule out the possibility that some patients who claimed never to have received an

antipsychotic may have nevertheless been pretreated. We consider this possibility unlikely given the early stage of the illness and the fact that we had good back-up information from relatives and patient records. Very extensive questioning about previous medication was a focus of the EUFEST study, so we can assume that under-reporting was very low. If there was any doubt, patients were excluded from the prolactin study. In addition, even if we made erroneous assumptions about some patients' pretreatment status, it would be difficult to explain our finding of a considerable increase in prolactin across the full sample.

Because prolactin levels were not measured in a central laboratory but rather in the individual study centers, there may have been some variation in absolute prolactin level differences. However, as all centers used immunoassays standardized against the 3rd International Reference Standard 84/500, the assessment of 'hyperprolactinemia' seems correct.

Prolactin secretion follows a circadian and ultradian rhythm and to a lesser extent depends on the phase of the menstrual cycle. Although centers were instructed to collect blood samples in the morning, there was no control for menstrual cycle-dependent variations in female patients, which may have contributed to variance in prolactin levels in females. However, apart from the magnitude of effects, we did find increased prolactin levels in both sexes.

Lastly, given our rigorous exclusion approach, we were left with a relatively small patient sample of truly antipsychotic-naïve individuals. At the same time, however, this rigorous approach is a strength of our study.

Conclusions

Clinically, our findings indicate that prolactin should be measured in patients with first-episode psychosis and putative prodromal states before the introduction of antipsychotics. In terms of research, our findings may contribute to explaining how stress may trigger the outbreak of schizophrenic psychoses: stress induces hyperprolactinemia that, through feedback, can increase dopamine. The latter is certainly speculative but should stimulate further research.

Appendix. EUFEST Study Group

Principal Investigators: R. S. Kahn, W. W. Fleischhacker. *Executive Committee:* R. S. Kahn, I. P. M. Keet (trial coordinator until July 2004), H. Boter (trial coordinator since July 2004). *Management Group:* R. S. Kahn, W. W. Fleischhacker, H. Boter, C. Brugman,

H. Burger, D. E. Grobbee, M. C. Hafkamp, I. P. M. Keet, K. Nijssen. *Steering Committee:* R. S. Kahn, W. W. Fleischhacker, H. Boter, I. P. M. Keet, C. Brugman, M. Davidson, S. Dollfus, W. Gaebel, S. Galderisi, M. Gheorghe, I. Gonen, D. E. Grobbee, L. G. Hranov, M. Hummer, J. Libiger, N. Lindefors, J. J. López-Ibor, K. Nijssen, J. Peuskens, A. Riecher-Rössler, J. K. Rybakowski, G. Sedvall, M. v. Wilmsdorff. *Office Manager:* P. C. Ywema. *Julius Centre Study Team: data management:* N. Boekema, H. den Breeijen, M. van den Haak, P. Huizinga, R. Veen; *project managers:* C. Brugman, M. C. Hafkamp, K. M. Nijssen; *site monitoring:* P. Berackova, A. Blizanowska, C. Brugman, M. C. Hafkamp, T. Huizinga, H. van Gelderen, M. Gordat, S. Lorteau, G. Makhlanlal, H. Moqadar. *Tangent Data Study Team (co-monitoring Romania):* I. Gonen, A. Mihailescu, R. Radici, C. Zus. *Participating investigators (CC=country coordinator; SC=site coordinator), centers, and countries:* Austria: M. Hummer (CC and SC Innsbruck), M. Muhlbacher (SC Salzburg), H. Widmoser (SC Hall in Tirol); Belgium: J. Peuskens (CC), J. Hulselmans (SC Antwerpen), C. Mertens (SC Gent), E. Thijs (SC Kortenberg); Bulgaria: L. G. Hranov (CC and SC Sofia), S. Georgiev (SC Plovdiv), L. Sayan (SC Bourgas); Czech Republic: J. Libiger (CC and SC Hradec Králové), E. Češková (SC Brno), D. Seifertová (SC Praha-Bohnice); France: S. Dollfus (CC and SC Caen I), G. Allio (SC Rouen), B. Chabot (SC Caen II), A. N. Coulaud (SC Dieppe), P. Thomas (SC Lille); Germany: W. Gaebel (CC), M. Krebs (SC Berlin), R. Lencer (SC Lübeck), K. Leopold (SC Berlin), T. Wobrock (SC Homburg); Israel: M. Davidson (CC), Y. Abramovitch (SC Beer-Yaakov), D. Amital (SC Ness Ziona), A. Caspi (SC Ramat Gan), A. Kaplan (SC Beer Sheva), I. Treves (SC Shalvata), P. Zipris (SC Pardessiya); Italy: S. Galderisi (CC), M. Casacchia (SC L'Aquila), G. Invernizzi (SC Milano II), A. Mucci (SC Naples), S. Scarone (SC Milano I), A. Vita (SC Melzo); The Netherlands: H. Boter (CC and SC Utrecht), I. P. M. Keet (CC and SC Utrecht); Poland: J. K. Rybakowski (CC and SC Poznan), M. Jarema (SC Warsaw), M. Masiak (SC Lublin), J. Rabe-Jablonska (SC Lodz); Romania: M. Gheorghe (CC), V. Burtea (SC Brasov), P. Boisteanu (SC Iasi), C. Friedman (SC Constanta), M. Ienciu (SC Timisoara), A. Ionescu (SC Buzau), I. Miclutia (SC Cluj), T. Mihai (SC Tulcea), D. Prelipceanu (SC Bucuresti II), T. Udistroiu (SC Craiova), D. Vasile (SC Bucuresti I); Spain: J. J. López-Ibor (CC), J. L. Carrasco (SC Madrid); Sweden: N. Lindefors (CC and SC Stockholm), G. Sedvall (CC), F. A. Wiesel (SC Uppsala); Switzerland: A. Riecher-Rössler (CC), U. Gschwandtner (SC Basel).

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Declaration of Interest

A.R.-R. has received unconditional grants from Eli Lilly, Janssen-Cilag, AstraZeneca, Bristol-Myers Squibb, Lundbeck and was advisory board member of Janssen-Cilag and Eli Lilly. J.K.R. has acted as a consultant or as a speaker for Adamed-Poland, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Lundbeck, Organon, Pfizer, Sanofi-Aventis, and Servier. R.S.K. has received grants, honoraria for education programs, or served as consultant for Astellas, AstraZeneca, BMS, Eli Lilly, Janssen-Cilag, Pfizer, Roche, and Sanofi-Aventis. W.W.F. receives research grants from Otsuka, Janssen, Reckitt Benckiser; has received consulting honoraria from Endo, Lundbeck, Roche, BMS, Otsuka, Janssen, Pfizer, Unitedbiosource, MedAvante, Sunovion, Merck; speaker honoraria from Lundbeck, Sunovion, Janssen, Eli Lilly, Otsuka, Roche; and owns MedAvante stocks.

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